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MEMORANDUM

SUBJECT: Critical Review of NCI 2,4-D Study

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TO: Anne Barton, Deputy Director  
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Attached is my review of the NCI 2,4-D study. I have also attached my earlier review of the protocol for this study which I sent to you on November 20, 1981, and my memo of concern relating to this study and others like it which I sent to John Melone June 2, 1983.

I have found that the present study does not provide sufficient evidence to conclude that 2,4-D is a likely cause of non-Hodgkin's lymphoma. However, the NCI study is, in many respects, a very strong study and I recommend that further studies of this kind be encouraged and supported. The evidence is currently inconclusive, but another well-done study might enable us to draw a much firmer conclusion.

Attachment

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Summary of Peer Review Comments

Agricultural Herbicide Use and Risk of Lymphoma and Soft-Tissue Sarcoma. Shelia Hoar, Aaron Blair, Frederick Holmes, Cathy Boysen, Robert Robel, Robert Hoover, and Joseph Fraumeni. Journal of the American Medical Association (JAMA) 256: 1141-1147, 1986.

Summary prepared by Jerome Blondell, Health Statistician  
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I. Introduction

A population-based, case-control study conducted by the National Cancer Institute in Kansas, found an association between farm herbicide use and non-Hodgkin's lymphoma (NHL) but did not find an association with soft-tissue sarcoma (STS) or Hodgkin's disease (HD). Four reviewers were asked to evaluate this study, particularly the weight of evidence for an association between 2,4-D and NHL. In addition, the editorial in JAMA which reviewed the evidence from various studies was found to be useful and is included here. The reviewers are:

1. Brian MacMahon, M.D., Ph.D., Professor of Epidemiology and Head of the Department, Harvard University, School of Public Health.
2. Martha Linet, M.D., M.P.H., Assistant Professor of Epidemiology, Johns Hopkins University, School of Hygiene and Public Health.
3. Donald Morgan, M.D., Ph.D., Professor of Preventive Medicine and Environmental Health, University of Iowa, College of Medicine.
4. Leon Burmeister, Ph.D., Professor of Biostatistics, University of Iowa, College of Medicine.
5. Theodore Colton, Sc.D., Boston University School of Public Health (editorial in JAMA).

This summary of reviewer comments will focus on the possible association between 2,4-D and NHL. The overall quality of the study, problems with exposure assessments and analysis will be addressed. Support from other studies, especially the one by Hardell in Sweden will also be covered (Hardell L., et al. Malignant lymphoma and exposure to chemicals especially organic

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solvents, chlorophenols and phenoxy acids: a case-control study British Journal of Cancer 43:169, 1981). Finally, the main conclusions of each reviewer will be summarized.

## II. Overall Quality of the Study

Reviewers disagree on the conclusions that could be drawn from the Hoar, et al. study but most agreed that it was of high quality and should serve as a basis for further research. MacMahon stated "This study shows every indication of having been carefully and competently carried out." Linet commented on "The overall excellent design and careful execution" and Burmeister noted that the study had "very high scientific validity." The editorial in JAMA praised the study for being "well designed and carefully executed." Hoar, et al. were commended for their population-based sample, use of histologically confirmed cases, high response rates, and the careful analysis of the results.

## III. Exposure Assessment

Strong concerns were expressed by all the reviewers regarding at least one major aspect of the exposure assessment. Key areas of concern were the use of next-of-kin interviews, lack of specific data on 2,4-D exposure, and the apparent underreporting of herbicide use.

Half of the NHL cases and the matched controls had died before the study had started. Therefore, it was necessary to use next-of-kin telephone interviews to assess the use of herbicides. Linet, Morgan and MacMahon commented on the lack of reliability likely to occur with next-of-kin interviews. MacMahon noted "one must question surrogates' knowledge of what specific herbicides were used and on how many days of the year." Morgan felt that "This kind of information cannot be accepted as reliable evidence of past chemical exposure."

Recall bias may exist among both live subjects and next-of-kin that would tend to favor the memory of those herbicides which had been used most frequently, most recently and had the easiest names to remember (e.g. 2,4,-D). This is especially a problem when trying to remember the names of chemicals used 30 or 40 years ago. In addition, there may be recall bias between cases and controls such that cases will try harder to remember what pesticides they were exposed to. In order to assess recall bias a sample (14%) of the suppliers who sold the pesticides were contacted. The degree of confirmation by the suppliers is only vaguely described by Hoar, et al., "suppliers usually reported less pesticide use than subjects," and "there were no consistent differences between agreement rates for patients and controls." Additional data on suppliers' responses have been requested from NCI but have not yet been provided.

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It is important to note that the frequency and duration of 2,4-D use was not specifically addressed by the Hoar, et al. study questionnaire. The questionnaire asks "About how many days per year were you usually exposed to herbicides . . . ?" Table 3 in the Hoar, et al. article seems to suggest that the results were specific for 2,4-D use, although a careful reading of the text indicates that this table refers to total herbicide use and not just 2,4-D. NCI has submitted a request for a correction statement to JAMA regarding the title of Table 3 to show that while only users of 2,4-D are included, the numbers given for duration and frequency refer to all herbicide use.

Two reviewers commented on the apparent underreporting of herbicide use by both cases and controls. Dr. Morgan's criticism was the strongest. While quoting from the Hoar, et al. study, he stated: "If 'these four crops constituted 94% of Kansas farm acreage and 87% of acres treated with herbicides' [in 1978] how does it happen that three-fourths [71%] of Kansas farmers interviewed hadn't used any herbicides at all on their farms? I submit that the exposure information acquired by telephone interview was worthless." Dr. MacMahon raised a similar point in our phone conversation after he had already submitted his review.

To examine this possibility further, I have examined six USDA reports on pesticide usage (covering the years 1952, 1958, 1964, 1966, 1971, and 1976) and one EPA survey in 1974. In 1976, USDA reported the usage of herbicides in the Northern Plains area, consisting of North Dakota, South Dakota, Nebraska, and Kansas. The percent of planted acreage treated with herbicides was 41% for wheat, 66% for sorghum and 84% for corn. USDA reported that 39% of all Kansas corn acreage and 5% of the acreage in small grains was treated with herbicides in 1958. In Kansas the reported estimates of herbicide use in 1974 on the four crops studied was 6.6 million pounds for the triazines, 2.4 million pounds for phenoxyacetic acids and 16,000 pounds for the uracils. But the percentage of cases and controls who had ever lived or worked on a farm reporting use of these chemicals was in reverse order; just 7% for the triazines, 13% for phenoxyacetic acids and 17% for the uracils. It is possible that other family members or hired commercial applicators may have applied these herbicides over the 30-40 year period. But the inconsistencies between the subjects' reported use in the Hoar, et al. study and the reported use in USDA and EPA surveys suggests a very serious potential for inaccurate reporting.

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#### IV. Analysis

Although significant trends and associations were found between herbicide exposure (based on duration or frequency of use) and NHL, two of the reviewers noted that these trends and associations were based on very small numbers. Only 2 of the 9 odds ratios were significant for NHL and either duration or frequency of herbicide use among those who reported using 2,4-D. Regarding farmers who used herbicides, MacMahon commented that "in the most persuasive category (use of 21 or more days per year), where there are 7 cases, the expected number based on the controls would be about 2.3. It would take only 2 or 3 cases misclassified to this category (or controls misclassified out of it) to render the difference not statistically (or biologically) significant." The significant odds ratio of 7.6 for frequent use of herbicides among those who used 2,4-D was based on only 5 cases. With such small numbers, only moderate amounts of misclassification of exposure would be needed to produce this result. And, as described in the previous section, such misclassification might easily have occurred.

In addition to frequency and duration, the analyses for latency, protective clothing, and method of application supported an association between NHL and herbicides. Unfortunately, this association was not specific only to herbicides or only to phenoxyacetic acids. Fungicides were also implicated as a risk factor for NHL; even after adjustment for herbicide use. And phenoxyacetic acids were not the only herbicides implicated. MacMahon noted "Among 8 groups of herbicides . . . [the odds ratio] associated with phenoxyacetic acid is lower than that for any other group except the uracils."

The NCI study chose controls that were matched on age, sex, and vital status, but not occupation. The odds ratio for simply living or working on a farm was 1.4 (nonsignificant), and a number of other studies have found that farming is a risk factor for NHL. Farmers have lifestyles that differ considerably from the general population. Their diet, smoking and drinking habits, physical activity, and hygiene are all examples of factors that may confound results when comparisons are made with the general population. In particular, farmers may be more exposed to viruses (a possible cause of lymphoma) as a result of being outdoors and exposed to livestock. Controlling for farming as an occupation would have helped to alleviate this potential source of confounding.

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## V. Evidence From Other Studies

Contradictory conclusions were reached by reviewers concerning support of the NCI findings by other studies, particularly the study by Hardell, et al. (see reference, page 1). Dr. Linet concluded "Although the Hardell, et al. study findings are greatly weakened by a number of substantial methodological problems, nevertheless the results support those of Hoar, et al." Dr. MacMahon reached an opposing conclusion: "I do not believe that the author's conclusion that the study confirms the reports from Sweden and several U.S. States that NHL is associated with farm pesticide use, especially phenoxy-acetic acids is justified." Dr. MacMahon explains part of his reasoning as follows:

"The important discrepancy is that the Swedish study found significant associations for all three tumors and the U.S. study only for one. Before concluding that the U.S. study is confirmatory of the Swedish one with respect to NHL, one must understand the reason for the discrepancy with respect to STS and HD. The reasons for these discrepancies--whether in the exposures studied, the method of study, or simply chance--are as cogent as is the agreement with respect to NHL. Until there is an adequate explanation for the discrepancies, one can have little confidence that the agreement represents reality." Dr. Morgan was also concerned about the reason for the discrepancy.

Dr. MacMahon goes on to conclude that "except when relative risks are high--and sometimes even then--no single study will establish an association between an exposure and an outcome. The acceptance of an association depends on a number of studies showing consistent results across populations and across different epidemiological methods. The study of Hoar, et al. is a strong study--strong enough on its own to establish a hypothesis of relationship of exposure to 2,4-D with some small proportion of cases of NHL."

Although Dr. Linet stated that the Hardell, et al. study was supportive, she felt that it was "plagued with a number of important methodologic limitations." Dr. Colton's editorial in JAMA supported this finding: "Selection bias, observation bias, and uncontrolled confounding loom as important points of vulnerability and, in fact, have emerged as the focus of sharp criticisms of the Hardell studies." Dr. Colton and Dr. Linet shared the concern raised by the Australia Royal Commission which reviewed Hardell's study and found that the intense media attention and Dr. Hardell's advocacy position in the media may have biased the results.

None of the other studies that were examined by the reviewers were felt to lend strong support to the findings of Hoar, et al.

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## VI. Reviewers Conclusions

Listed below are the final conclusions of each reviewer relative to the 2,4-D/NHL association. Dr. Colton did not have a conclusion on this particular point.

### Dr. MacMahon

"In my opinion the weight of evidence does not support the conclusion that there is an association between exposure to 2,4-D and NHL."

### Dr. Linet

"In the opinion of this reviewer, the weight of the scientific evidence is beginning to lean towards possible causation between herbicide exposure, particularly 2,4-D, and development of non-Hodgkin's lymphoma in farmers . . . it would seem to be prudent to consider the possibility of temporarily substantially limiting or even banning the use of 2,4-D until ongoing studies have been completed."

### Dr. Morgan

"I don't believe the "weight of evidence" indicates any excess risk of lymphoma among agricultural workers exposed to 2,4-D."

### Dr. Burmeister

"It is my opinion that we can not say 2,4-D is a cause of lymphoma based on epidemiological studies. The "weight of evidence" should be limited to educating users about the cautions necessary to reduce to the likely risks of 2,4-D."

## Reviewer's Conclusion

As both Drs. Linet and MacMahon point out, more than one study is needed to establish an association. These two reviewers disagreed on the level of support from other studies, particularly the Hardell study. Moreover serious questions have been raised about the accuracy of the exposure data, which when combined with the misclassification likely from next-of-kin interviews and the small numbers of 2,4-D users, could completely change the results. To be sure that herbicides and not some other lifestyle factor (e.g. viruses) were not responsible for the findings, the authors should have controlled for farming occupation in their analysis.

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In my opinion, the Hoar, et al. study does not provide sufficient evidence to support a credible causal interpretation concerning 2,4-D and NHL. Misclassification of exposure, chance and inadequate control of confounding factors might easily have created the apparent association. Other studies were not strong enough or consistent enough to support this finding of association. I cannot tell from the definitions given in the Guidelines for Carcinogen Risk Assessment whether this study should fall under category number two, "limited evidence of carcinogenicity," or category three, "inadequate evidence."





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